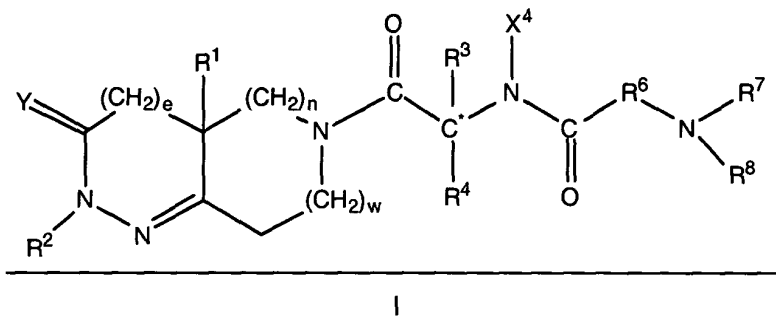


AMENDMENTS TO THE CLAIMS

Claims 1-6 (canceled)

7. (currently amended) A method for treating insulin resistance in a mammal which comprises administering to said mammal an effective amount of a compound of formula I



or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers, or the pharmaceutically acceptable salts and prodrugs thereof,

wherein

e is 0 or 1;

n and w are each independently 0, 1 or 2;

provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R¹ is hydrogen, -CN, -(CH₂)_qN(X⁶)C(O)X⁶, -(CH₂)_qN(X⁶)C(O)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)SO₂(CH₂)_t-A¹, -(CH₂)_qN(X⁶)SO₂X⁶, -(CH₂)_qN(X⁶)C(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)C(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qC(O)OX⁶, -(CH₂)_qC(O)O(CH₂)_t-A¹, -(CH₂)_qOX⁶, -(CH₂)_qOC(O)X⁶, -(CH₂)_qOC(O)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(X⁶), -(CH₂)_qC(O)X⁶, -(CH₂)_qC(O)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)C(O)OX⁶, -(CH₂)_qN(X⁶)SO₂N(X⁶)(X⁶), -(CH₂)_qS(O)_mX⁶, -(CH₂)_qS(O)_m(CH₂)_t-A¹, -(C₁-C₁₀)alkyl, -(CH₂)_t-A¹, -(CH₂)_q-(C₃-C₇)cycloalkyl, -(CH₂)_q-Y¹-(C₁-C₆)alkyl, -(CH₂)_q-Y¹-(CH₂)_t-A¹ or -(CH₂)_q-Y¹-(CH₂)_t-(C₃-C₇)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R¹ are optionally substituted with (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂,

-S(O)_m(C₁-C₆)alkyl, -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y¹ is O, S(O)_m, -C(O)NX⁶-, -CH=CH-, -C≡C-, -N(X⁶)C(O)-, -C(O)NX⁶-,

-C(O)O-, -OC(O)N(X⁶)- or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said (CH₂)_q group and (CH₂)_t group may each be optionally substituted with hydroxyl,

(C₁-C₄)alkoxy, carboxyl, -CONH₂, -S(O)_m(C₁-C₆)alkyl,

-CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C₁-C₄)alkyl;

R² is hydrogen, (C₁-C₆)alkyl, -(C₀-C₃)alkyl-(C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl-A¹ or A¹;

where the alkyl groups and the cycloalkyl groups in the definition of R² are optionally substituted with hydroxyl, -C(O)OX⁶, -C(O)N(X⁶)(X⁶), -N(X⁶)(X⁶),

-S(O)_m(C₁-C₆)alkyl, -C(O)A¹, -C(O)(X⁶), CF₃, CN or 1, 2 or 3 halogen;

R³ is A¹, (C₁-C₁₀)alkyl, -(C₁-C₆)alkyl-A¹, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl,

-(C₁-C₅)alkyl-X¹-(C₁-C₅)alkyl, -(C₁-C₅)alkyl-X¹-(C₀-C₅)alkyl-A¹ or

-(C₁-C₅)alkyl-X¹-(C₁-C₅)alkyl-(C₃-C₇)cycloalkyl;

where the alkyl groups in the definition of R³ are optionally substituted with

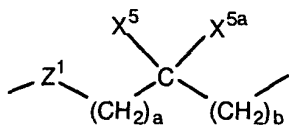
-S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX³;

X¹ is O, S(O)_m, -N(X²)C(O)-, -C(O)N(X²)-, -OC(O)-, -C(O)O-, -CX²=CX²-,

-N(X²)C(O)O-, -OC(O)N(X²)- or -C≡C-;

R⁴ is hydrogen, (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl, or R⁴ is taken together with R³ and the carbon atom to which they are attached and form (C₅-C₇)cycloalkyl, (C₅-C₇)cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X⁴ is hydrogen or (C₁-C₆)alkyl or X⁴ is taken together with R⁴ and the nitrogen atom to which X⁴ is attached and the carbon atom to which R⁴ is attached and form a five to seven membered ring;



R⁶ is a bond or is

where a and b are independently 0, 1, 2 or 3;

X⁵ and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A¹ and optionally substituted (C₁-C₆)alkyl;

the optionally substituted (C₁-C₆)alkyl in the definition of X⁵ and X^{5a} is optionally substituted with a substituent selected from the group consisting of A¹, OX², -S(O)_m(C₁-C₆)alkyl, -C(O)OX², (C₃-C₇)cycloalkyl, -N(X²)(X²) and -C(O)N(X²)(X²);

or the carbon bearing X⁵ or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R⁷ and R⁸ wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X⁵ or X^{5a} but not both may be on the carbon atom and R⁷ or R⁸ but not both may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X⁵ and X^{5a} cannot be on the carbon atom and R⁷ and R⁸ cannot be on the nitrogen atom;

or X⁵ is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X⁵ is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z¹ is a bond, O or N-X², provided that when a and b are both 0 then Z¹ is not N-X² or O;

R⁷ and R⁸ are independently hydrogen or optionally substituted (C₁-C₆)alkyl;

where the optionally substituted (C₁-C₆)alkyl in the definition of R⁷ and R⁸ is optionally independently substituted with A¹, -C(O)O-(C₁-C₆)alkyl,

-S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 -O-C(O)(C₁-C₁₀)alkyl or 1 to 3 (C₁-C₆)alkoxy; or

R⁷ and R⁸ can be taken together to form -(CH₂)_r-L-(CH₂)_r;

where L is C(X²)(X²), S(O)_m or N(X²);

A¹ for each occurrence is independently (C₅-C₇)cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially

saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A¹ for each occurrence is independently optionally substituted, in one or optionally both rings if A¹ is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF₃, OCF₂H, CF₃, CH₃, OCH₃, -OX⁶, -C(O)N(X⁶)(X⁶), -C(O)OX⁶, oxo, (C₁-C₆)alkyl, nitro, cyano, benzyl, -S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶), -N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹², -NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;

the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is optionally independently substituted with phenyl, phenoxy, (C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-C₆)alkoxy;

X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X¹² is not hydrogen, X¹² is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;

or X¹¹ and X¹² are taken together to form -(CH₂)_{L¹}-(CH₂)_{L¹};

where L¹ is C(X²)(X²), O, S(O)_m or N(X²);

r for each occurrence is independently 1, 2 or 3;

X² for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X² are optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5 halogens or 1-3 OX³;

X³ for each occurrence is independently hydrogen or (C₁-C₆)alkyl;

X⁶ is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, (C₃-C₇)-halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X⁶ is optionally independently substituted by 1 or 2 (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl, carboxylate (C₁-C₄)alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X⁶ groups on one atom and both X⁶ are independently (C₁-C₆)alkyl, the two (C₁-C₆)alkyl groups may be optionally joined and, together with the atom to which the two X⁶ groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX⁷;

X⁷ is hydrogen or (C₁-C₆)alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

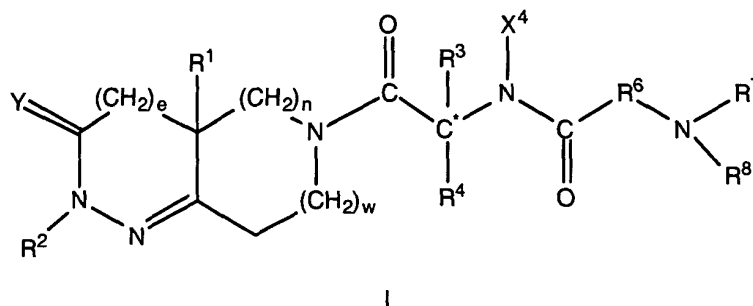
with the proviso that:

X⁶ and X¹² cannot be hydrogen when it is attached to C(O) or SO₂ in the form C(O)X⁶, C(O)X¹², SO₂X⁶ or SO₂X¹²; and

when R⁶ is a bond then L is N(X²) and each r in the definition -(CH₂)_r-L-(CH₂)_r- is independently 2 or 3; wherein the method ~~according to claim 1~~ which additionally comprises administering to a mammal in need thereof a growth hormone releasing hormone or a functional analog thereof.

8. (canceled)

9. (original) A method for increasing levels of endogenous growth hormone, which comprises administering to a human or other animal in need thereof effective amounts of a functional somatostatin antagonist and a compound of formula I



or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers or the pharmaceutically acceptable salts and prodrugs thereof,

wherein

e is 0 or 1;

n and w are each independently 0, 1 or 2;

provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R¹ is hydrogen, -CN, -(CH₂)_qN(X⁶)C(O)X⁶, -(CH₂)_qN(X⁶)C(O)(CH₂)_r-A¹,

-(CH₂)_qN(X⁶)SO₂(CH₂)_r-A¹, -(CH₂)_qN(X⁶)SO₂X⁶, -(CH₂)_qN(X⁶)C(O)N(X⁶)(CH₂)_r-A¹,

$-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_tA^1$,
 $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_tA^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$,
 $-(CH_2)_qOC(O)(CH_2)_tA^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_tA^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$,
 $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_tA^1$, $-(CH_2)_qN(X^6)C(O)OX^6$,
 $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_tA^1$,
 $-(C_1-C_{10})alkyl$, $-(CH_2)_tA^1$, $-(CH_2)_q-(C_3-C_7)cycloalkyl$, $-(CH_2)_q-Y^1-(C_1-C_6)alkyl$,
 $-(CH_2)_q-Y^1-(CH_2)_tA^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)cycloalkyl$;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with $(C_1-C_4)alkyl$, hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $-CONH_2$,

$-S(O)_m(C_1-C_6)alkyl$, $-CO_2(C_1-C_4)alkyl$ ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6$, $-CH=CH-$, $-C\equiv C-$, $-N(X^6)C(O)-$, $-C(O)NX^6$,

$-C(O)O-$, $-OC(O)N(X^6)-$ or $-OC(O)-$;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)alkyl$,

$-CO_2(C_1-C_4)alkyl$ ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 $(C_1-C_4)alkyl$;

R^2 is hydrogen, $(C_1-C_6)alkyl$, $-(C_0-C_3)alkyl-(C_3-C_6)cycloalkyl$, $-(C_1-C_4)alkyl-A^1$ or A^1 ;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$,

$-S(O)_m(C_1-C_6)alkyl$, $-C(O)A^1$, $-C(O)(X^6)$, CF_3 , CN or 1, 2 or 3 halogen;

R^3 is A^1 , $(C_1-C_{10})alkyl$, $-(C_1-C_6)alkyl-A^1$, $-(C_1-C_6)alkyl-(C_3-C_7)cycloalkyl$,

$-(C_1-C_5)alkyl-X^1-(C_1-C_5)alkyl$, $-(C_1-C_5)alkyl-X^1-(C_0-C_5)alkyl-A^1$ or

$-(C_1-C_5)alkyl-X^1-(C_1-C_5)alkyl-(C_3-C_7)cycloalkyl$;

where the alkyl groups in the definition of R^3 are optionally substituted with

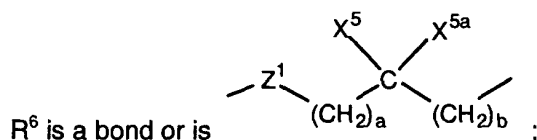
$-S(O)_m(C_1-C_6)alkyl$, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3 ;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$,

$-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, $(C_1-C_6)alkyl$ or $(C_3-C_7)cycloalkyl$, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form $(C_5-C_7)cycloalkyl$, $(C_5-C_7)cycloalkenyl$, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X⁴ is hydrogen or (C₁-C₆)alkyl or X⁴ is taken together with R⁴ and the nitrogen atom to which X⁴ is attached and the carbon atom to which R⁴ is attached and form a five to seven membered ring;



where a and b are independently 0, 1, 2 or 3;

X⁵ and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A¹ and optionally substituted (C₁-C₆)alkyl;

the optionally substituted (C₁-C₆)alkyl in the definition of X⁵ and X^{5a} is optionally substituted with a substituent selected from the group consisting of A¹, OX², -S(O)_m(C₁-C₆)alkyl, -C(O)OX², (C₃-C₇)cycloalkyl, -N(X²)(X²) and -C(O)N(X²)(X²);

or the carbon bearing X⁵ or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R⁷ and R⁸ wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X⁵ or X^{5a} but not both may be on the carbon atom and R⁷ or R⁸ but not both may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X⁵ and X^{5a} cannot be on the carbon atom and R⁷ and R⁸ cannot be on the nitrogen atom;

or X⁵ is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X⁵ is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z¹ is a bond, O or N-X², provided that when a and b are both 0 then Z¹ is not N-X² or O;

R⁷ and R⁸ are independently hydrogen or optionally substituted (C₁-C₆)alkyl;

where the optionally substituted (C₁-C₆)alkyl in the definition of R⁷ and R⁸ is optionally independently substituted with A¹, -C(O)O-(C₁-C₆)alkyl,

$-\text{S}(\text{O})_m(\text{C}_1-\text{C}_6)\text{alkyl}$, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-\text{O}-\text{C}(\text{O})(\text{C}_1-\text{C}_{10})\text{alkyl}$ or 1 to 3 $(\text{C}_1-\text{C}_6)\text{alkoxy}$; or

R^7 and R^8 can be taken together to form $-(\text{CH}_2)_r-\text{L}-(\text{CH}_2)_r-$;

where L is $\text{C}(\text{X}^2)(\text{X}^2)$, $\text{S}(\text{O})_m$ or $\text{N}(\text{X}^2)$;

A^1 for each occurrence is independently $(\text{C}_5-\text{C}_7)\text{cycloalkenyl}$, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3 , OCF_2H , CF_3 , CH_3 , OCH_3 , $-\text{OX}^6$, $-\text{C}(\text{O})\text{N}(\text{X}^6)(\text{X}^6)$, $-\text{C}(\text{O})\text{OX}^6$, oxo, $(\text{C}_1-\text{C}_6)\text{alkyl}$, nitro, cyano, benzyl, $-\text{S}(\text{O})_m(\text{C}_1-\text{C}_6)\text{alkyl}$, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-\text{N}(\text{X}^6)(\text{X}^6)$, $-\text{N}(\text{X}^6)\text{C}(\text{O})(\text{X}^6)$, $-\text{SO}_2\text{N}(\text{X}^6)(\text{X}^6)$, $-\text{N}(\text{X}^6)\text{SO}_2\text{-phenyl}$, $-\text{N}(\text{X}^6)\text{SO}_2\text{X}^6$, $-\text{CONX}^{11}\text{X}^{12}$, $-\text{SO}_2\text{NX}^{11}\text{X}^{12}$, $-\text{NX}^6\text{SO}_2\text{X}^{12}$, $-\text{NX}^6\text{CONX}^{11}\text{X}^{12}$, $-\text{NX}^6\text{SO}_2\text{NX}^{11}\text{X}^{12}$, $-\text{NX}^6\text{C}(\text{O})\text{X}^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted $(\text{C}_1-\text{C}_6)\text{alkyl}$;

the optionally substituted $(\text{C}_1-\text{C}_6)\text{alkyl}$ defined for X^{11} is optionally independently substituted with phenyl, phenoxy, $(\text{C}_1-\text{C}_6)\text{alkoxycarbonyl}$, $-\text{S}(\text{O})_m(\text{C}_1-\text{C}_6)\text{alkyl}$, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $(\text{C}_1-\text{C}_{10})\text{alkanoyloxy}$ or 1 to 3 $(\text{C}_1-\text{C}_6)\text{alkoxy}$;

X^{12} is hydrogen, $(\text{C}_1-\text{C}_6)\text{alkyl}$, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3 , OCH_3 , OCF_3 and CF_3 ;

or X^{11} and X^{12} are taken together to form $-(\text{CH}_2)_r-\text{L}^1-(\text{CH}_2)_r-$;

where L^1 is $\text{C}(\text{X}^2)(\text{X}^2)$, O, $\text{S}(\text{O})_m$ or $\text{N}(\text{X}^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6) alkyl, or optionally substituted (C_3-C_7) cycloalkyl, where the optionally substituted (C_1-C_6) alkyl and optionally substituted (C_3-C_7) cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1-3 OX^3 ;

X^3 for each occurrence is independently hydrogen or (C_1-C_6) alkyl;

X^6 is independently hydrogen, optionally substituted (C_1-C_6) alkyl, (C_2-C_6) halogenated alkyl, optionally substituted (C_3-C_7) cycloalkyl, (C_3-C_7) -halogenatedcycloalkyl, where optionally substituted (C_1-C_6) alkyl and optionally substituted (C_3-C_7) cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 (C_1-C_4) alkyl, hydroxyl, (C_1-C_4) alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$ alkyl, carboxylate (C_1-C_4) alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6) alkyl, the two (C_1-C_6) alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 ;

X^7 is hydrogen or (C_1-C_6) alkyl optionally substituted with hydroxyl; and

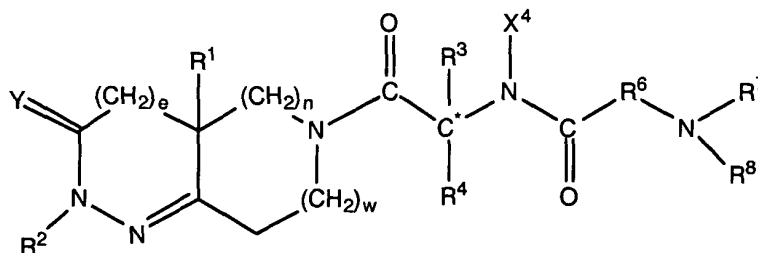
m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to $C(O)$ or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12} ; and

when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is independently 2 or 3.

10. (original) A method of treating or preventing congestive heart failure, obesity or frailty associated with aging, which comprises administering to a mammal in need thereof effective amounts of a functional somatostatin antagonist and a compound of formula I



I

or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers or the pharmaceutically acceptable salts and prodrugs thereof,

wherein

e is 0 or 1;

n and w are each independently 0, 1 or 2;

provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R¹ is hydrogen, -CN, -(CH₂)_qN(X⁶)C(O)X⁶, -(CH₂)_qN(X⁶)C(O)(CH₂)_t-A¹,
-(CH₂)_qN(X⁶)SO₂(CH₂)_t-A¹, -(CH₂)_qN(X⁶)SO₂X⁶, -(CH₂)_qN(X⁶)C(O)N(X⁶)(CH₂)_t-A¹,
-(CH₂)_qN(X⁶)C(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(CH₂)_t-A¹,
-(CH₂)_qC(O)OX⁶, -(CH₂)_qC(O)O(CH₂)_t-A¹, -(CH₂)_qOX⁶, -(CH₂)_qOC(O)X⁶,
-(CH₂)_qOC(O)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(X⁶),
-(CH₂)_qC(O)X⁶, -(CH₂)_qC(O)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)C(O)OX⁶,
-(CH₂)_qN(X⁶)SO₂N(X⁶)(X⁶), -(CH₂)_qS(O)_mX⁶, -(CH₂)_qS(O)_m(CH₂)_t-A¹,
-(C₁-C₁₀)alkyl, -(CH₂)_t-A¹, -(CH₂)_q-(C₃-C₇)cycloalkyl, -(CH₂)_q-Y¹-(C₁-C₆)alkyl,
-(CH₂)_q-Y¹-(CH₂)_t-A¹ or -(CH₂)_q-Y¹-(CH₂)_t-(C₃-C₇)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R¹ are optionally substituted
with (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂,

-S(O)_m(C₁-C₆)alkyl, -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y¹ is O, S(O)_m, -C(O)NX⁶-, -CH=CH-, -C≡C-, -N(X⁶)C(O)-, -C(O)NX⁶-,

-C(O)O-, -OC(O)N(X⁶)- or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said (CH₂)_q group and (CH₂)_t group may each be optionally substituted with hydroxyl,
(C₁-C₄)alkoxy, carboxyl, -CONH₂, -S(O)_m(C₁-C₆)alkyl,

-CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C₁-C₄)alkyl;

R² is hydrogen, (C₁-C₈)alkyl, -(C₀-C₃)alkyl-(C₃-C₈)cycloalkyl, -(C₁-C₄)alkyl-A¹ or A¹;

where the alkyl groups and the cycloalkyl groups in the definition of R² are optionally
substituted with hydroxyl, -C(O)OX⁶, -C(O)N(X⁶)(X⁶), -N(X⁶)(X⁶),

-S(O)_m(C₁-C₆)alkyl, -C(O)A¹, -C(O)(X⁶), CF₃, CN or 1, 2 or 3 halogen;

R³ is A¹, (C₁-C₁₀)alkyl, -(C₁-C₆)alkyl-A¹, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl,

-(C₁-C₅)alkyl-X¹-(C₁-C₅)alkyl, -(C₁-C₅)alkyl-X¹-(C₀-C₅)alkyl-A¹ or

-(C₁-C₅)alkyl-X¹-(C₁-C₅)alkyl-(C₃-C₇)cycloalkyl;

where the alkyl groups in the definition of R³ are optionally substituted with

-S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX³;

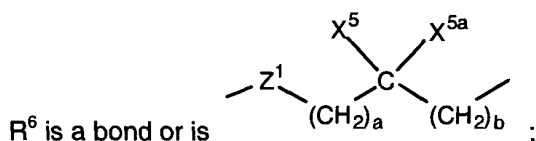
X¹ is O, S(O)_m, -N(X²)C(O)-, -C(O)N(X²)-, -OC(O)-, -C(O)O-, -CX²=CX²-,

-N(X²)C(O)O-, -OC(O)N(X²)- or -C≡C-;

R⁴ is hydrogen, (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl, or R⁴ is taken together with R³ and the
carbon atom to which they are attached and form (C₅-C₇)cycloalkyl, (C₅-C₇)cycloalkenyl, a

partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_6) alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;



where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted (C_1-C_6) alkyl;

the optionally substituted (C_1-C_6) alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1 , OX^2 , $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^2$, (C_3-C_7) cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X^5 or X^{5a} but not both may be on the carbon atom and R^7 or R^8 but not both may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4

heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z¹ is a bond, O or N-X², provided that when a and b are both 0 then Z¹ is not N-X² or O;

R⁷ and R⁸ are independently hydrogen or optionally substituted (C₁-C₆)alkyl;

where the optionally substituted (C₁-C₆)alkyl in the definition of R⁷ and R⁸ is optionally independently substituted with A¹, -C(O)O-(C₁-C₆)alkyl,

-S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 -O-C(O)(C₁-C₁₀)alkyl or 1 to 3 (C₁-C₆)alkoxy; or

R⁷ and R⁸ can be taken together to form -(CH₂)_r-L-(CH₂)_r;

where L is C(X²)(X²), S(O)_m or N(X²);

A¹ for each occurrence is independently (C₅-C₇)cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A¹ for each occurrence is independently optionally substituted, in one or optionally both rings if A¹ is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF₃, OCF₂H, CF₃, CH₃, OCH₃, -OX⁶,

-C(O)N(X⁶)(X⁶), -C(O)OX⁶, oxo, (C₁-C₆)alkyl, nitro, cyano, benzyl,

-S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶),

-N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹²,

-NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and tetrazolyl,

provided that if A¹ is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;

the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is optionally independently substituted with phenyl, phenoxy, (C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-C₆)alkoxy;

X^{12} is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

where L^1 is $C(X^2)(X^2)$, O, S(O)_m or N(X^2);

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X^2 are optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5 halogens or 1-3 OX³;

X^3 for each occurrence is independently hydrogen or (C₁-C₆)alkyl;

X^6 is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, (C₃-C₇)-halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl, carboxylate (C₁-C₄)alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C₁-C₆)alkyl, the two (C₁-C₆)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX⁷;

X^7 is hydrogen or (C₁-C₆)alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO₂ in the form C(O)X⁶, C(O)X¹², SO₂X⁶ or SO₂X¹²; and

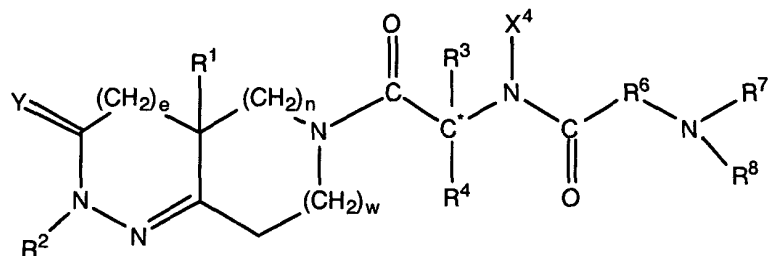
when R⁶ is a bond then L is N(X^2) and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is independently 2 or 3.

11. (original) A method according to claim 10 wherein said functional somatostatin antagonist is an alpha-2 adrenergic agonist.

12. (original) A method according to claim 11 wherein said alpha-2 adrenergic agonist is selected from the group consisting of clonidine, xylazine and medetomidine.

13. (original) A method according to claim 12 wherein said compound of formula I is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide L-tartaric acid salt.

14. (original) A pharmaceutical composition which comprises a pharmaceutically acceptable carrier, an amount of an alpha-2 adrenergic agonist and an amount of a compound of formula I



I

or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers or the pharmaceutically acceptable salts and prodrugs thereof,

wherein

e is 0 or 1;

n and w are each independently 0, 1 or 2;

provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R¹ is hydrogen, -CN, -(CH₂)_qN(X⁶)C(O)X⁶, -(CH₂)_qN(X⁶)C(O)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)SO₂(CH₂)_t-A¹, -(CH₂)_qN(X⁶)SO₂X⁶, -(CH₂)_qN(X⁶)C(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)C(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qC(O)OX⁶, -(CH₂)_qC(O)O(CH₂)_t-A¹, -(CH₂)_qOX⁶, -(CH₂)_qOC(O)X⁶, -(CH₂)_qOC(O)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(X⁶), -(CH₂)_qC(O)X⁶, -(CH₂)_qC(O)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)C(O)OX⁶, -(CH₂)_qN(X⁶)SO₂N(X⁶)(X⁶), -(CH₂)_qS(O)_mX⁶, -(CH₂)_qS(O)_m(CH₂)_t-A¹, -(C₁-C₁₀)alkyl, -(CH₂)_t-A¹, -(CH₂)_q-(C₃-C₇)cycloalkyl, -(CH₂)_q-Y¹-(C₁-C₆)alkyl, -(CH₂)_q-Y¹-(CH₂)_t-A¹ or -(CH₂)_q-Y¹-(CH₂)_t-(C₃-C₇)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R¹ are optionally substituted with (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂,

-S(O)_m(C₁-C₆)alkyl, -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y¹ is O, S(O)_m, -C(O)NX⁶-, -CH=CH-, -C≡C-, -N(X⁶)C(O)-, -C(O)NX⁶-,

-C(O)O-, -OC(O)N(X⁶)- or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, (C_1-C_4) alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$ alkyl,

$-CO_2(C_1-C_4)$ alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C_1-C_4) alkyl;

R^2 is hydrogen, (C_1-C_8) alkyl, $-(C_0-C_3)$ alkyl- (C_3-C_8) cycloalkyl, $-(C_1-C_4)$ alkyl- A^1 or A^1 ;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$,

$-S(O)_m(C_1-C_6)$ alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3 , CN or 1, 2 or 3 halogen;

R^3 is A^1 , (C_1-C_{10}) alkyl, $-(C_1-C_6)$ alkyl- A^1 , $-(C_1-C_6)$ alkyl- (C_3-C_7) cycloalkyl,

$-(C_1-C_5)$ alkyl- X^1 - (C_1-C_5) alkyl, $-(C_1-C_5)$ alkyl- X^1 - (C_0-C_5) alkyl- A^1 or

$-(C_1-C_5)$ alkyl- X^1 - (C_1-C_5) alkyl- (C_3-C_7) cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with

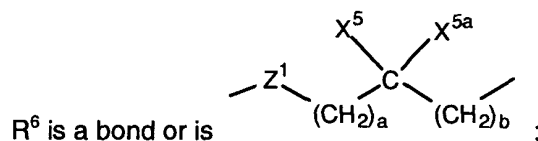
$-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3 ;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$,

$-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, (C_1-C_6) alkyl or (C_3-C_7) cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form (C_5-C_7) cycloalkyl, (C_5-C_7) cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_6) alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;



where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted (C_1-C_6) alkyl;

the optionally substituted (C_1-C_6) alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of

A^1 , OX^2 , $-S(O)_m(C_1-C_6)alkyl$, $-C(O)OX^2$, $(C_3-C_7)cycloalkyl$, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X^5 or X^{5a} but not both may be on the carbon atom and R^7 or R^8 but not both may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or $N-X^2$, provided that when a and b are both 0 then Z^1 is not $N-X^2$ or O;

R^7 and R^8 are independently hydrogen or optionally substituted $(C_1-C_6)alkyl$;

where the optionally substituted $(C_1-C_6)alkyl$ in the definition of R^7 and R^8 is optionally independently substituted with A^1 , $-C(O)O-(C_1-C_6)alkyl$,

$-S(O)_m(C_1-C_6)alkyl$, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O-C(O)(C_1-C_{10})alkyl$ or 1 to 3 $(C_1-C_6)alkoxy$; or

R^7 and R^8 can be taken together to form $-(CH_2)_r-L-(CH_2)_r-$;

where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

A^1 for each occurrence is independently $(C_5-C_7)cycloalkenyl$, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4

heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A¹ for each occurrence is independently optionally substituted, in one or optionally both rings if A¹ is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF₃, OCF₂H, CF₃, CH₃, OCH₃, -OX⁶,
-C(O)N(X⁶)(X⁶), -C(O)OX⁶, oxo, (C₁-C₆)alkyl, nitro, cyano, benzyl,
-S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶),
-N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹²,
-NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;

the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is optionally independently substituted with phenyl, phenoxy, (C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-C₆)alkoxy;

X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X¹² is not hydrogen, X¹² is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;

or X¹¹ and X¹² are taken together to form -(CH₂)_r-L¹-(CH₂)_r;

where L¹ is C(X²)(X²), O, S(O)_m or N(X²);

r for each occurrence is independently 1, 2 or 3;

X² for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X² are optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5 halogens or 1-3 OX³;

X³ for each occurrence is independently hydrogen or (C₁-C₆)alkyl;

X⁶ is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, (C₃-C₇)-halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X⁶ is optionally independently substituted by 1 or 2 (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl, carboxylate (C₁-C₄)alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6) alkyl, the two (C_1-C_6) alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 ;

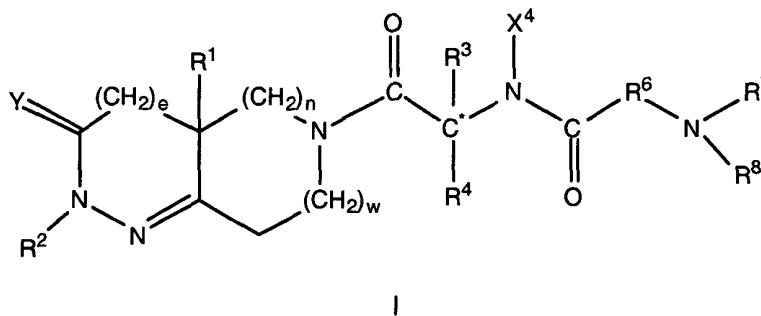
X^7 is hydrogen or (C_1-C_6) alkyl optionally substituted with hydroxyl; and
m for each occurrence is independently 0, 1 or 2;
with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to $C(O)$ or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12} ; and

when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is independently 2 or 3.

Claims 15-25 (canceled)

26. (original) A method of treating sleep disorders in a mammal suffering from sleep disorders comprising administering to said mammal an effective amount of a compound of formula I



or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers, or the pharmaceutically acceptable salts and prodrugs thereof,

wherein

e is 0 or 1;

n and w are each independently 0, 1 or 2;

provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R^1 is hydrogen, $-CN$, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_tA^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_tA^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_tA^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)X^6$, $-(CH_2)_qC(O)N(X^6)X^6$, $-(CH_2)_qC(O)N(X^6)(CH_2)_tA^1$,

$-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_tA^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$,
 $-(CH_2)_qOC(O)(CH_2)_tA^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_tA^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$,
 $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_tA^1$, $-(CH_2)_qN(X^6)C(O)OX^6$,
 $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_tA^1$,
 $-(C_1-C_{10})alkyl$, $-(CH_2)_tA^1$, $-(CH_2)_q-(C_3-C_7)cycloalkyl$, $-(CH_2)_q-Y^1-(C_1-C_6)alkyl$,
 $-(CH_2)_q-Y^1-(CH_2)_tA^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)cycloalkyl$;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with $(C_1-C_4)alkyl$, hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $-CONH_2$,

$-S(O)_m(C_1-C_6)alkyl$, $-CO_2(C_1-C_4)alkyl$ ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6$, $-CH=CH-$, $-C\equiv C-$, $-N(X^6)C(O)-$, $-C(O)NX^6$,

$-C(O)O-$, $-OC(O)N(X^6)-$ or $-OC(O)-$;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)alkyl$,

$-CO_2(C_1-C_4)alkyl$ ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 $(C_1-C_4)alkyl$;

R^2 is hydrogen, $(C_1-C_8)alkyl$, $-(C_0-C_3)alkyl-(C_3-C_8)cycloalkyl$, $-(C_1-C_4)alkyl-A^1$ or A^1 ;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$,

$-S(O)_m(C_1-C_6)alkyl$, $-C(O)A^1$, $-C(O)(X^6)$, CF_3 , CN or 1, 2 or 3 halogen;

R^3 is A^1 , $(C_1-C_{10})alkyl$, $-(C_1-C_6)alkyl-A^1$, $-(C_1-C_6)alkyl-(C_3-C_7)cycloalkyl$,

$-(C_1-C_5)alkyl-X^1-(C_1-C_5)alkyl$, $-(C_1-C_5)alkyl-X^1-(C_0-C_5)alkyl-A^1$ or

$-(C_1-C_5)alkyl-X^1-(C_1-C_5)alkyl-(C_3-C_7)cycloalkyl$;

where the alkyl groups in the definition of R^3 are optionally substituted with

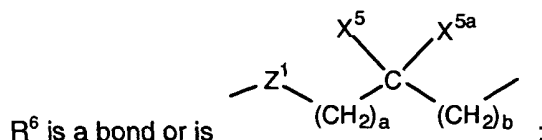
$-S(O)_m(C_1-C_6)alkyl$, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3 ;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$,

$-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, $(C_1-C_6)alkyl$ or $(C_3-C_7)cycloalkyl$, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form $(C_5-C_7)cycloalkyl$, $(C_5-C_7)cycloalkenyl$, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X⁴ is hydrogen or (C₁-C₆)alkyl or X⁴ is taken together with R⁴ and the nitrogen atom to which X⁴ is attached and the carbon atom to which R⁴ is attached and form a five to seven membered ring;



where a and b are independently 0, 1, 2 or 3;

X⁵ and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A¹ and optionally substituted (C₁-C₆)alkyl;

the optionally substituted (C₁-C₆)alkyl in the definition of X⁵ and X^{5a} is optionally substituted with a substituent selected from the group consisting of A¹, OX², -S(O)_m(C₁-C₆)alkyl, -C(O)OX², (C₃-C₇)cycloalkyl, -N(X²)(X²) and -C(O)N(X²)(X²);

or the carbon bearing X⁵ or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R⁷ and R⁸ wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X⁵ or X^{5a} but not both may be on the carbon atom and R⁷ or R⁸ but not both may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X⁵ and X^{5a} cannot be on the carbon atom and R⁷ and R⁸ cannot be on the nitrogen atom;

or X⁵ is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X⁵ is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z¹ is a bond, O or N-X², provided that when a and b are both 0 then Z¹ is not N-X² or O;

R⁷ and R⁸ are independently hydrogen or optionally substituted (C₁-C₆)alkyl;

where the optionally substituted (C₁-C₆)alkyl in the definition of R⁷ and R⁸ is optionally independently substituted with A¹, -C(O)O-(C₁-C₆)alkyl,

-S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 -O-C(O)(C₁-C₁₀)alkyl or 1 to 3 (C₁-C₆)alkoxy; or

R⁷ and R⁸ can be taken together to form -(CH₂)_r-L-(CH₂)_r;

where L is C(X²)(X²), S(O)_m or N(X²);

A¹ for each occurrence is independently (C₅-C₇)cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A¹ for each occurrence is independently optionally substituted, in one or optionally both rings if A¹ is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF₃, OCF₂H, CF₃, CH₃, OCH₃, -OX⁶,

-C(O)N(X⁶)(X⁶), -C(O)OX⁶, oxo, (C₁-C₆)alkyl, nitro, cyano, benzyl,

-S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶),

-N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹²,

-NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;

the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is optionally independently substituted with phenyl, phenoxy, (C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-C₆)alkoxy;

X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X¹² is not hydrogen, X¹² is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;

or X¹¹ and X¹² are taken together to form -(CH₂)_r-L¹-(CH₂)_r;

where L¹ is C(X²)(X²), O, S(O)_m or N(X²);

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X^2 are optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5 halogens or 1-3 OX³;

X^3 for each occurrence is independently hydrogen or (C₁-C₆)alkyl;

X^6 is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, (C₃-C₇)-halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl, carboxylate (C₁-C₄)alkyl ester, or 1H-tetrazol-5-yl; or when there are two X^6 groups on one atom and both X^6 are independently (C₁-C₆)alkyl, the two (C₁-C₆)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX⁷;

X^7 is hydrogen or (C₁-C₆)alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO₂ in the form C(O)X⁶, C(O)X¹², SO₂X⁶ or SO₂X¹²; and

when R⁶ is a bond then L is N(X²) and each r in the definition -(CH₂)_r-L-(CH₂)_r- is independently 2 or 3.